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IN THIS ISSUE

Focus of the Month:
Dual Diagnosis in Addiction Medicine

Learning Objectives
After reading these articles, you should be able to:

1. Identify effective treatment options for managing substance-related agitation in acute settings.
2. Determine how to assess and treat co-occurring psychiatric disorders and substance use disorders.
3. Recognize cognitive behavioral therapy techniques for patients with substance use disorders.
4. Summarize some of the current findings in the literature regarding substance use disorder treatment.

Managing Substance-Related Agitation

Thomas Jordan, MD, MPH. Contributing writer to the Carlat newsletters.

Dr. Jordan has disclosed that he has no relevant financial or other interests in any commercial companies pertaining to this educational activity.

In emergency departments, psychiatrists are often consulted on patients presenting with agitation. In many cases, these patients are under the influence of substances—either from intoxication or withdrawal. It is important to recognize when a patient is under these effects, as acute management of the agitation will vary drastically depending on which substances have been used. In this article, I'll share some tips gleaned from my experience in managing these patients, as well as information from the

In Summary

- Assessing physical signs and symptoms and appropriate laboratory tests can help clinicians diagnose and manage agitation in patients with substance intoxication or withdrawal.
- Agitation resulting from alcohol withdrawal requires immediate treatment with a benzodiazepine if accompanied by grand mal seizures or delirium.
- Though often effective in controlling agitation, antipsychotics should be used cautiously in patients with substance withdrawal or intoxication due to lowering of the seizure threshold.

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Q&A With the Expert

Treating Co-Occurring Psychiatric Disorders

Stephen Ross, MD

Associate Professor of Psychiatry and Child & Adolescent Psychiatry at New York University School of Medicine. Director of Addiction Psychiatry, NYU Tisch Hospital.

Dr. Ross has disclosed that he has no relevant financial or other interests in any commercial companies pertaining to this educational activity.

CATR: Why do you think clinicians should pay attention to psychiatric disorders co-occurring with addiction?

Dr. Ross: The reason is that they're very common. For example, about 80% of people with schizophrenia have nicotine use disorder, and 50% have a non-nicotine substance use disorder (SUD) (Miller SC, Fiellin DA, Rosenthal RN, Saitz R, eds. *ASAM Principles of Addiction Medicine.* 6th ed. Philadelphia, PA: Wolters Kluwer, 2019:1401–1417). And just about any psychiatric disorder has a higher rate of addiction comorbidity than in the general population. The rates are even higher in treatment settings—more than 50% of people in addiction treatment settings will have a co-occurring psychiatric problem, and more than 50% in psychiatric settings will typically have a co-occurring SUD (https://tinyurl.com/y3fly9u2). The treatment outcome is going to be poor if you're not addressing the addiction part, which is often missed if clinicians don't look for it. It's important to recognize this multiplicity of diagnoses so you can form a treatment plan that addresses both psychiatric and addiction issues using all available tools.

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research literature. For more detailed information on emergency psychiatry, I recommend an excellent recent text published by the APA (Riba MB, Ravindranath D, Winder GS, eds. *Clinical Manual of Emergency Psychiatry*. 2nd rev ed. Arlington, VA: American Psychiatric Association Publishing; 2015).

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Evaluation

Whenever a patient presents with agitation, substance misuse is high on my differential diagnosis list. I ask both the patient and collateral contacts about substances, and I order a urine drug screen (UDS), which is cheap, relatively quick, and can change my clinical management. Some patients act offended when asked to provide a sample, but I explain that it's part of my routine protocol. Know what is included in your hospital's UDS, as different laboratories will test for slightly different drug metabolites or give you varying degrees of sensitivity and specificity. For example, some tests include buprenorphine while others don't, and some break down a positive benzodiazepine screen into specific medications (though this usually takes a few days). Serum drug testing can also be done for substances not included on the standard UDS and can give you quantitative data, but this takes longer. In addition to the UDS, I will typically do a brief physical exam focused on signs of substance use, such as elevated vital signs, disordered gait, tremor, slurred speech, and dilated or pinpoint pupils. I also perform a skin examination for sweating, gooseflesh, and track marks.

Alcohol

We've all had patients arrive at the emergency department late at night smelling of alcohol. Agitation in these patients can be caused by either alcohol intoxication or alcohol withdrawal. The treatment of most alcohol intoxication is largely supportive, letting a patient "sleep it off." However, very high alcohol levels can cause decreased body temperature, blood pressure, and respirations while triggering reflex tachycardia, all of which will generally be managed by the emergency department physician. As blood alcohol levels begin to drop, start looking for alcohol withdrawal. In some people with chronic alcohol use disorder, withdrawal can start as soon as 6 hours after the last drink. Someone who came into the emergency department as pleasantly inebriated may wake up combative, yelling, and demanding to leave. You should be familiar with the symptoms of alcohol withdrawal, characterized by sweating, increased blood pressure and heart rate, anxiety, tremors, nausea, and vomiting. In severe cases you may see grand mal seizures, delirium, and hallucinations, which require immediate intervention (Goodson CM, *Alcohol Clin Exp Res* 2014;38(10):2664–2677). Standard treatment is with a benzodiazepine such as diazepam or lorazepam, or phenobarbital (which can then be tapered). In cases of severe agitation or psychosis not responding to a benzodiazepine, an antipsychotic with low anticholinergic activity such as haloperidol can be used, but it is important to avoid overmedicating and lowering the seizure threshold. And remember that IV hydration combined with IV thiamine (oral thiamine has poor absorption) can prevent Wernicke-Korsakoff syndrome and long-term neurological problems (Latt N and Dore G, *Intern Med J* 2014;44(9):911–915).

Benzodiazepines

Like alcohol, benzodiazepines act on GABA receptors, and the same general principles apply. However, different benzodiazepines will have different durations of action and half-lives, thus varying the timeline of the intoxication and withdrawal period. Intoxication solely with benzodiazepines is rarely lethal in otherwise healthy adults, but it can cause fatal respiratory depression when combined with opioids, alcohol, or other CNS depressants. Flumazenil is an antidote for benzodiazepines, but it should be given carefully only to those in respiratory depression, as it may shift the patient into immediate withdrawal and seizures. Treatment for benzodiazepine withdrawal is largely the same as for alcohol, but be aware that

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some longer-acting benzodiazepines like clonazepam can have a withdrawal period of weeks to months and are best tapered over a similar time period.

Opioids

As the opioid epidemic continues, emergency departments have become accustomed to treating opioid withdrawal, which causes agitation related to anxiety and general discomfort. Recognize the telltale signs of opioid withdrawal, including large pupils, runny nose, sweating, gooseflesh, yawning, anxiety, nausea, vomiting, diarrhea, and muscle aches. Unlike alcohol or benzodiazepine withdrawal, opioid withdrawal is rarely lethal by itself, but it may be life-threatening in medically compromised individuals. It's now the standard of care to provide treatment for opioid withdrawal in emergency settings, not only to address the accompanying discomfort but also to create a bridge to addiction treatment. Buprenorphine is an opioid partial agonist that can quickly relieve the effects of withdrawal. Only give buprenorphine to someone already experiencing at least some withdrawal, as its action will cause immediate withdrawal in someone who is still intoxicated. Other medications can be given for mild withdrawal symptoms, including clonidine and other symptom-triggered treatments, such as NSAIDs for muscle aches, loperamide for diarrhea, trazodone for sleep, and hydroxyzine for anxiety. Benzodiazepines can be helpful in controlling agitation and anxiety, but they should be used with caution. Remember that patients are at greater risk for overdose directly after tapering off of opioids (Davoli M et al, *Addiction* 2007;102(12):1954–1959). As such, it's important to be familiar with the resources available for transition to buprenorphine, methadone, or extended-release naltrexone.

Stimulants

Intoxication with direct CNS stimulants is a common cause of severe agitation in emergency settings. Commonly misused CNS stimulants include cocaine, methamphetamine, 3,4-methylenedioxymethamphetamine (MDMA or ecstasy), and prescription amphetamines. You can identify intoxication by large pupils, tremors, increased heart rate, blood pressure, respirations, and hyperreflexia. Severe intoxication can cause seizures, paranoid delusions, and hallucinations (typically tactile or visual). There is a risk of heart attack or stroke, especially in people who already have cardiovascular risk factors. Always be aware of other substances the patient may be using, such as the combination of alcohol and cocaine—which produces cocaethylene, a potent and long-acting metabolite that carries more risk of sudden death. First-line treatment for agitation from stimulants is to induce sedation with a benzodiazepine. Even if there is psychosis present, benzodiazepines are still preferred, as antipsychotic medications may lower the seizure threshold and may contribute to cardiac arrhythmias and hyperthermia—though this is still under debate in the emergency medicine literature (Connors NJ et al, *Am J Emerg Med* 2019;pii:S0735-6757(19)30001–30004). Other medications to avoid include beta-blockers, as there is a theoretical risk of worsening hypertension and cardiovascular problems due to an unopposed alpha-adrenergic response.

PCP

Phencyclidine (PCP or angel dust) use has declined since the 1970s, but you may still see dramatic presentations of PCP intoxication. This synthetic substance is an NMDA receptor antagonist and inhibits the reuptake of dopamine, norepinephrine, and serotonin. It is often not included in standard UDS tests, so diagnosis may depend on your clinical skills. Be on the lookout for psychiatric symptoms of anxiety, paranoia, hallucinations, retrograde amnesia, and disorientation, combined with physical symptoms of hypertension, tachycardia, and horizontal or vertical nystagmus (Dominici P et al, *J Med Toxicol* 2015;11(3):321–325). The psychosis of a PCP intoxication can closely mimic that seen in an acute episode of schizophrenia. Patients may act on paranoid and bizarre delusions with violent behavior toward themselves or others, made more severe due to the decreased response to pain caused by PCP. However, in other individuals, PCP may cause catatonia or stupor, leading to a comatose state that can be severe enough to require intubation. Medical complications usually come from rhabdomyolysis, seizures, or a prolonged comatose state. Agitation control follows similar guidance to that of CNS stimulants—benzodiazepines are preferred to induce sedation, and antipsychotics are to be used with caution due to lowering of the seizure threshold.

Designer drugs

Similar to PCP, some designer drugs can also lead to acute agitation combined with psychosis. This category includes synthetic cannabinoids such as K2 or spice, as well as synthetic cathinones, commonly referred to as bath salts or incense. There are various other street names for these substances, and they don't usually show up on a UDS. The clinical presentation can be quite dramatic, with severe agitation, mania, and hallucinations, combined with medical complications of electrolyte disturbances, delirium, hypothermia, seizures, and serotonin syndrome (Klega AE and Keehbauch JT, *Am Fam Physician* 2018;98(2):85–92). If you suspect that a patient is on one of these designer drugs, use benzodiazepines as first-line treatment for agitation, and again use caution with antipsychotics due to lowering of the seizure threshold (Jerry J et al, *Cleve Clin J Med* 2012;79(4):258–264).

CATR VERDICT: Evaluation of the agitated patient in an emergency setting can be challenging, even more so when the agitation is due to substance use. Physical signs and symptoms, laboratory testing, and a thorough collection of history and collateral information are the keys to correct diagnosis. Tailor the treatment to the specific substance responsible for the intoxication or withdrawal, and regularly monitor for changes in the patient's presentation.

Cognitive Behavioral Therapy for Substance Use Disorders

Cognitive behavioral therapy (CBT) is one of the most widely used psychotherapies. It was developed in the 1960s by Aaron Beck specifically for the treatment of depression, but its core principles were quickly adapted and applied to a variety of diagnoses. We now have evidence-based CBT interventions not only for depression but also for anxiety, PTSD, bipolar disorder, obesity, insomnia, and substance use disorders (SUDs). Here we'll go through the basic framework of CBT, how it can be applied to SUDs, and ways to incorporate parts of CBT into your daily addiction treatment practice.

CBT overview

The general treatment approach of CBT is to identify problematic thoughts and behaviors, evaluate what is contributing to those thoughts and behaviors, and then apply new skills to change the outcome of a given situation (Beck JS. *Cognitive Behavior Therapy: Basics and Beyond.* 2nd ed. New York, NY: Guildford Press; 2011). Through this process, negative or irrational core beliefs are identified and then changed over time to positive or rational beliefs. For example, the thought "I am terrible at everything and others are better than me" may become "I have strengths and weaknesses, just like other people." CBT is problem-focused, meaning that a patient identifies specific areas of improvement and generally works on one problem or situation at a time. CBT is also present-oriented; it does not focus on past developmental experiences. The therapist can be directive, taking on the role of a teacher for skills training. The classic CBT model of individual or group-based therapy takes place over about 12 structured sessions, but the concepts we'll discuss here can also be used in brief medication management visits.

CBT applied to SUDs

When CBT is applied for the treatment of SUDs, several common treatment themes usually emerge, no matter which substance is being used (McHugh RK et al, *Psychiatr Clin North Am* 2010;33(3): 511–525). The key components of CBT that are helpful in treating SUDs are functional analysis, which is identifying triggers and high-risk situations, and skill building. Together the provider and patient can pinpoint maladaptive behavior patterns, barriers to change, and skill deficits. Examples include identifying high-risk situations, like driving by a liquor store; a related skill that can be developed may involve taking a different route (avoiding) or reciting reasons to quit when passing by the store (coping). G. Alan Marlatt's relapse prevention therapy incorporates these aspects of CBT into initiating and maintaining positive behavior change; it has been used to treat SUDs for decades (Hendershot CS et al, *Subst Abuse Treat Prev Policy* 2011;6:17). One common method of skill building involves role-playing exercises between the provider and patient. For instance, the patient may identify a high-risk situation at school or work that involves pressure to use substances. The provider can take on the role of the fellow student or coworker while the patient practices different ways of handling the situation.

12-step programs commonly use CBT techniques when dealing with external and internal triggers for substance use (https://sobernation.com). For external triggers, think of people, places, and things: social contacts the patient hung out with, the place the patient was buying or using drugs, and things associated with the drug use like paraphernalia or favorite drinking glasses. External triggers can even be sensory, like sounds or smells the patient associates with drug use. Internal triggers can be explained using the 12-step acronym of HALT: Hunger, Anger, Lonely, and Tired—all common states that can trigger use. When a craving occurs, patients should stop and evaluate whether they are in one of the HALT states, and then take steps to fix the HALT situation instead of turning to substances. This requires using the CBT techniques of identifying the behavior pattern (functional analysis) and then substituting a positive behavior for the negative one (skill building). For instance, carrying around healthy snacks can stop hunger, having go-to meditation exercises can soothe anger, reaching out to a trusted friend or sponsor can address loneliness, and napping or taking time to relax can help deal with feeling tired.

Does it work?

Do these CBT interventions actually work to decrease a patient's substance use? The evidence for CBT has been mounting since the 1980s, and a 2009 meta-analysis looked at 53 studies of CBT specifically for SUDs (Magill M and Ray LA, *J Stud Alcohol Drugs* 2009;70:516–527). Across all studies, there was a small but significant effect size of 0.144, $p < 0.005$. When breaking the studies down for type of substance, CBT had a small significant treatment effect for each, except for marijuana use where the effect size was moderate at 0.513, $p < 0.005$. Effect sizes increased when CBT was combined with other psychosocial treatment (0.305, $p < 0.005$) or with medication management (0.208, $p < 0.005$). The largest effect size of 0.796, $p < 0.005$, was seen with the studies that compared CBT to no treatment at all.

Incorporating CBT into your practice

While many of your patients may not have the time or resources to attend a course of structured CBT sessions, there are many ways to incorporate CBT concepts into your daily practice. When patients are in the early stages of change, motivational interviewing can bring them closer to the action stage, and then CBT techniques can be used to learn and practice specific skills to promote and maintain recovery. This can be as simple as asking about triggers for their substance use (functional analysis), then thinking about ways of avoiding or coping with those triggers (skill building). Other skills that can be improved upon in a brief clinical visit include communication skills with friends and family, coping skills for emotional regulation, identifying pleasurable sober activities to replace substance use, and goal-setting (eg, deciding on a quit date). Also, know when to refer a patient for a full CBT course. If you have someone who is ready to learn new skills, capitalize

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Expert Interview – Treating Co-Occurring Psychiatric Disorders
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CATR: Any thoughts on why comorbidity is so common?

Dr. Ross: There are different plausible explanations. One is the self-medication hypothesis. Drugs, if used acutely, can be very potent psychopharmacologic tools. They make people feel good, and they are used in an attempt to treat an underlying symptom. However, they have enormous side effects, including addiction. You can also argue that people with certain psychiatric disorders may have dopaminergic deficiencies in the parts of the brain involved in the reward system. There are also certain substances that cause long-term psychiatric issues. So, if people drink alcohol very heavily over decades, they can develop enough damage to cause a chronic cognitive or psychotic disorder, even if they stop drinking.

CATR: Does the self-medication hypothesis mean that by treating the psychiatric problem early, we may prevent addiction from developing?

Dr. Ross: The self-medication hypothesis is not perfect, but there is something to it. Let's say you take ADHD—40% to 50% of people with ADHD will develop a drug problem. Even more will develop tobacco addiction, and there are good data that, if you treat somebody with ADHD with a stimulant, it either decreases the patient's longitudinal risk of developing an SUD or does not increase the risk (Miller SC, Fiellin DA, Rosenthal RN, Saitz R, eds. *ASAM Principles of Addiction Medicine.* 6th ed. Philadelphia, PA: Wolters Kluwer, 2019:1418–1435). Another example is co-occurring major depressive disorder (MDD) and alcohol use disorder (AUD). The data show that treatment with antidepressants may not independently get the patient to drink less, but if the antidepressant works for the depression, then secondarily the drinking gets better. But none of this means that by just getting at the psychiatric problem, everything will flow downhill and the addiction will go away. You would hope there would be some benefit, but you also independently must treat the addiction. You would never treat co-occurring disorders with just a psychopharm agent for the psychiatric problem and hope the whole thing gets better.

"Taking a careful patient and family history, evaluating the severity of illness, and following somebody longitudinally can all help sort out whether a patient has a co-occurring illness or substance-induced disorder."

Stephen Ross, MD

CATR: Any advice on diagnosing comorbid psychiatric disorders? And specifically, how do you differentiate between primary and substance-induced disorders?

Dr. Ross: The main thing is you want to take a very careful longitudinal history, and you want to establish temporally what came first. If you get a clear history of patients who had depression in their 20s and addiction in their 30s, and they were depressed for many years without ever being addicted, you can rule in that they have an independent depressive spectrum disorder. But, it's often more complicated, and you may get patients who say, "I've been depressed and drinking forever." In that situation you would want to help them get abstinent and observe them for a period. Family history can also help; if there's strong family history for MDD, that points to a primary disorder. Another thing is symptom severity—if somebody meets 9 out of 9 criteria of major depression and gets suicidal, or gets psychotic depression, the severity there speaks to the fact that the patient probably has underlying MDD independently. So, careful history, family history, severity of illness, and following somebody longitudinally can all help sort out whether this is a co-occurring or a substance-induced illness.

CATR: Are there general medication strategies you'd recommend for treating co-occurring disorders?

Dr. Ross: You want to match the medications to the patient's needs to maximize adherence. This is true for all patients, but it may be even more pressing in people with both addiction and psychiatric issues. So, if somebody has psychosis and tends to not take medications, you'd want to give the patient a long-acting injectable formulation if you could. You can also think of an anti-addictive agent with an extended duration of action, such as extended-release naltrexone (Vivitrol) or the new formulation of subcutaneous buprenorphine. Another strategy is to directly observe taking the medication. Antabuse is an amazing medicine, but patients often stop taking it. So, if you build in that somebody will take it in the office, 3 times a week for example, you can enhance adherence. And the other thing is to treat early and treat aggressively.

CATR: Do you have advice on choice of meds for specific psychiatric disorders co-occurring with addiction?

Dr. Ross: Overall, you want something that can affect symptom domains in both disorders. For instance, if somebody has MDD and tobacco addiction, you'd think of bupropion, which can treat both. If you have bipolar disorder in adults, lithium may not be the best choice in patients that have co-occurring addiction. This may be because people with addiction are more likely to have mixed and rapid cycling features, and they seem to respond better to valproic acid (Cipriani A et al, *Cochrane Database Syst Rev* 2013;10:CD003196). If somebody has bipolar disorder and co-occurring substance use, I would think of valproic acid over lithium as a first-line treatment.

CATR: Are there data on treating co-occurring schizophrenia?

Dr. Ross: If you have schizophrenia that co-occurs with an SUD, you would want to consider starting with an atypical over a typical antipsychotic. This is because although the data are somewhat mixed, there is evidence that the atypicals are superior to typical antipsychotics in patients with co-occurring schizophrenia and an SUD, and there are data to suggest that typical antipsychotics are either not associated with decreased substance use or may actually make it worse (Miller SC, Fiellin DA, Rosenthal RN, Saitz R, eds. *ASAM Principles of Addiction Medicine.* 6th ed. Philadelphia, PA: Wolters Kluwer, 2019:1401–1417). In contrast, there are data for several atypical antipsychotics (ie, clozapine, risperidone, olanzapine, and aripiprazole) being associated with

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both a reduction in psychotic symptoms and substance use in this dually diagnosed cohort. Of the atypicals, the best data are for clozapine. Of course, you may not start with clozapine because of the side effects. But overall, you'd want to go with atypicals before you would use a typical.

CATR: What about comorbid anxiety? Should we avoid benzos?

Dr. Ross: Yes. If you have an anxiety disorder and a co-occurring substance problem, you do not want to use benzos as first-line agents. You would want to use an antidepressant like an SSRI or an SNRI and try a course of cognitive behavioral therapy (CBT). You'd also want to try psychotherapy, especially for PTSD, because none of the meds work particularly well for PTSD.

CATR: Are there situations when you would add a benzo?

Dr. Ross: You'd want to get the patient abstinent before considering a benzo. But let's say you've tried SSRIs and CBT, and the patient is still highly symptomatic and is abstinent. In this situation, you could potentially treat the patient with clonazepam, which is a benzo with relatively low addictive liability, and conduct close monitoring. There are no hard and fast rules. Some people say you should never give an addictive substance to somebody with addiction, and that's just not true because there are certain situations like the one I mentioned.

CATR: There's also the issue of whether to prescribe stimulants for ADHD co-occurring with addiction. What are your thoughts on that?

Dr. Ross: The first step would be to get the patient abstinent. You might want to start with something like atomoxetine or clonidine. But if that doesn't work and the patient is abstinent, then you could, with careful monitoring and a contract, prescribe the stimulant. You'd also give the patient an extended-release formulation, to lower the risk of misuse.

CATR: What about patients who continue to use cocaine, for example, and yet do have ADHD? Would you then intervene with a stimulant, or would you prescribe it only if the patient is sober?

Dr. Ross: I would make it contingent on the patient being sober, because if someone has ADHD and has, let's say, an alcohol and a cocaine problem, this patient is at high risk of having a seizure. And if you're adding another stimulant on top of that, you could do a lot of harm. I would say to the patient, "I will not give it to you until we have a stable recovery plan." If the patient is in stable recovery and still highly symptomatic after everything you've tried for the ADHD, at that point I would consider a stimulant. You'd also want to provide close monitoring: one week at a time, regular urine drug screens, and a treatment contract.

CATR: Going back to the antidepressants, there are some data on the effect of SSRIs on drinking based on age of onset of AUD. Should we take that into consideration when choosing an antidepressant?

Dr. Ross: Yes, there is an old literature that people with early-onset alcoholism have more family history of addiction and tend to have antisocial traits, and that SSRIs can worsen their drinking. Not all the studies show that, but there are enough to suggest something might be going on there. And there's also the literature on antisocial personality and serotonergic dysfunction, so we have a plausible biological explanation for how SSRIs may be further disrupting serotonergic pathways that are making the antisocial issues and the drinking worse. So, in somebody with early-onset alcoholism, I may not use an SSRI as a first-line medication. I would try something with a different mechanism of action, like mirtazapine.

CATR: We've mostly spoken about meds so far. Any advice on choosing the right psychotherapy for co-occurring addiction and psychiatric disorders?

Dr. Ross: Similar to choosing the right psychopharm agent, ideally you want to pick something that targets symptoms of both. For example, for patients with borderline personality disorder and co-occurring addiction, there are data from controlled trials that dialectical behavior therapy can decrease symptoms of both. This approach has not always panned out, though—there was dual focus schema therapy that Sam Ball developed at Yale, with the idea of treating the personality problem and the addiction, but it did not end up showing effectiveness for both. But even if the data aren't too robust for these combined psychotherapies, you want to think of a psychotherapy strategy that can address both diagnoses. So, if someone has depression and addiction, you can use CBT principles to target both problems. And you want to make sure the patient is in the appropriate level of care and is getting all psychopharm and psychosocial treatments in the appropriate dose over a long-enough period. Addiction is a chronic illness, and you need a long-term treatment plan.

CATR: Yes, we often hear about integrating treatment. What do you think about doing it sequentially instead, by first treating one disorder then the other one?

Dr. Ross: It can be hard to access, but the literature's very clear that integrated treatment outperforms sequential or parallel treatment (https://store.samhsa.gov/system/files/theevidence-itc.pdf). In the integrated model, you don't treat the addiction first and then hope to treat the psychiatric disorder later, or treat the psychiatric disorder first and then the addiction—you treat both in the same setting aggressively early on. The data show that patients do better with integrated care models than with treatment delivered sequentially or in parallel. Parallel means going to one place to get addiction treatment and then to a different place to get psychiatric treatment. It's better if everything is delivered in the same setting at the same time.

CATR: Any additional advice for clinicians treating co-occurring disorders?

Dr. Ross: Clinicians should remember that patients with co-occurring illnesses are very treatable—the trick is getting the right components in an integrated setting. Patients labeled as "treatment refractory" usually have not gotten anywhere close to the correct diagnosis or integrated care. And when they do get that correct care, they tend to do well. We have so many effective tools, and it's important that we integrate them in the right ways.

CATR: Thank you for your time, Dr. Ross.

Q&A With the Expert

Co-Occurring Addiction and PTSD

Dolores Vojvoda, MD

Assistant Professor of Psychiatry, Yale School of Medicine

Dr. Vojvoda has disclosed that she has no relevant financial or other interests in any commercial companies pertaining to this educational activity.

CATR: We know PTSD often co-occurs with addiction. What should clinicians pay attention to?

Dr. Vojvoda: Individuals who have PTSD have a high risk of developing other disorders, including substance use disorders (SUDs). Studies have shown that both in the veteran and non-veteran populations, these numbers are high. For example, one study of the general population found that alcohol use disorder (AUD) is the most common co-occurring disorder in men with PTSD (Kessler RC et al, *Arch of Gen Psychiatry* 1995;52(12):1048–1060). And a study in Vietnam veterans found that around 74% of combat veterans have an SUD (Kulka RA, Schlenger WE, Fairbank JA, et al. *Trauma and the Vietnam War Generation: Report of Findings From the National Vietnam Veterans Readjustment Study.* New York, NY: Brunner/Mazel; 1990). And this goes in the other direction as well—when we look at treatment-seeking populations with SUDs, we find that the rates of comorbidity with PTSD are higher compared to the general population. So, almost 63% of veterans with an SUD have comorbid PTSD (Seal KH et al, *J Gen Intern Med* 2011;26(10):1160–1167).

CATR: The take-home message, then, is that it's important to screen for these disorders.

Dr. Vojvoda: Exactly. Now, the complicating factor is that it's not only a matter of simple comorbidity—these impairments are more than the sum of their parts. Individuals that have both PTSD and SUDs have worse outcomes, including higher rates of other mental health disorders, medical problems, and functional impairment across multiple domains. They're more likely to be unemployed, they're more likely to be homeless, and they're also more likely to be hospitalized. Also, patients who have comorbid PTSD and SUDs often end up having more severe PTSD symptoms than patients with PTSD alone. So, when treating this population, we must keep in mind that we are probably seeing people who will need more help for more severe symptoms than patients with PTSD or SUD alone.

CATR: As clinicians, we often wonder whether addiction leads to trauma or trauma leads to addiction. What are your thoughts?

Dr. Vojvoda: I don't have a definite answer for that. We do know that substance use and PTSD tend to go hand in hand, and it's still unclear in which direction causality works. More importantly though, we know that co-occurrence increases severity of both disorders, and therefore we need to tackle both and not get derailed by overthinking which disorder came first. Historically, people were treating these disorders separately, even in different treatment settings, but now we find that such an approach is not as effective as the integrated treatment of both disorders.

CATR: Should treatment be provided by one clinician or by a team of clinicians who work together?

Dr. Vojvoda: It can be either. For a while there was a perception that addressing trauma would make substance use worse. Clinicians were reluctant to do trauma-focused psychotherapy in dually diagnosed patients and would wait until the SUD got better, but that would often lead to patient dropout or relapse because factors that were driving substance use were still present. With the appreciation that postponing treatment of either disorder can lead to poorer outcomes for both, people are now treating both disorders simultaneously and having much better treatment outcomes.

CATR: How early can we provide this integrated approach in the recovery process?

Dr. Vojvoda: In cases of patients with SUD who are at risk of withdrawal, detox and adequate medical stabilization need to be the first step in the treatment process. It is important to remember that PTSD can intensify the severity of withdrawal symptoms. But as soon as that acute phase of "detoxification" is over, we should start thinking of the best ways to integrate treatments. We know from several studies that trauma-focused psychotherapies can be tolerated even in the early phases of addiction treatment—there are a couple of studies with prolonged exposure (PE) and cognitive processing therapy (CPT) that were utilized along with psychotherapy for SUDs (Simpson TL et al, *Alcohol Clin Exp Res* 2017;41(4):681–702). We know from research that doing treatment this way benefits patients by reducing both PTSD symptoms and substance use.

CATR: Could you tell us more about trauma-focused psychotherapies?

Dr. Vojvoda: Trauma-focused psychotherapies use different techniques to help process the traumatic experience and may involve talking, thinking, or visualizing the traumatic memory; they may also focus on changing distorted beliefs about the trauma. We have the strongest evidence right now for CPT, PE, and eye movement desensitization and reprocessing (EMDR). All three of them seem to be effective in addressing both acute and chronic PTSD symptoms. These are manualized treatments, usually between 8 and 16 sessions long, and the therapist requires training to provide them.

CATR: What are the main differences between these three therapies?

Dr. Vojvoda: These therapies use cognitive, emotional, and behavioral techniques in the treatment of consequences of a traumatic event. Exposure to the traumatic event is a central to all these therapies. PE includes repeated exposure, both supervised recollection and in vivo, to the components of the traumatic event. CPT also includes a written exposure component but primarily focuses on modifying maladaptive beliefs about the trauma. And EMDR is also exposure-based and involves imaginal exposure to trauma accompanied by side-to-side eye movements or other bilateral stimuli like sound or hand tapping.

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Expert Interview – Co-Occurring Addiction and PTSD
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CATR: Is the eye-movement component to EMDR necessary, or is it just a gimmick?
Dr. Vojvoda: EMDR has evolved over the years. The eye movement component was initially considered a crucial part of treatment. However, in recent years there has been increased evidence that the eye movements do not play a significant role in the effectiveness of EMDR. Regardless of this controversy, EMDR has shown strong evidence as an effective treatment for PTSD.

CATR: I've also heard that CPT works even without a prominent exposure element. Is that true?
Dr. Vojvoda: CPT can be delivered with a written trauma account (CPT) or without a written trauma account (CPT-cognitive only, or CPT-C). It can be provided for patients who find it too difficult to talk about the trauma. Evidence shows that, in many cases, it is just as effective as the CPT with the exposure component (Walter KH et al, *J Trauma Stress* 2014;27(4):438–445).

CATR: We also hear about using mindfulness in treating PTSD. What are your thoughts on that?
Dr. Vojvoda: Mindfulness-based psychotherapies have not been traditionally seen as treatments for PTSD, but they are gaining momentum, especially as adjunctive treatments. Mindfulness involves awareness of the present moment, and being non-judgmental and accepting. We don't know empirically how effective these treatments are, but there are many reports of beneficial effects. Some patients find mindfulness helpful in regulating emotions and decreasing anxiety, depression, and impulsivity. It also helps with treatment engagement. And in people who are using substances, mindfulness may help cope with urges.

"Trauma-focused psychotherapies such as cognitive processing therapy (CPT), prolonged exposure (PE), and eye movement desensitization and reprocessing (EMDR) can be tolerated even in the early phases of addiction treatment. Doing treatment this way benefits patients by reducing both acute and chronic PTSD symptoms as well as substance use."

Dolores Vojvoda, MD

CATR: Should we start by evaluating what the patient can tolerate before offering trauma-focused psychotherapies?
Dr. Vojvoda: Yes. The first step is to evaluate the needs of the patient sitting across from you. So, if you have a patient who is unsure about starting trauma-based treatments, or whose biggest problem is regulating emotions, or who is unsure about being able to follow through with the weekly treatment, you may want to start with a treatment that addresses those issues first. For example, we may recommend dialectical behavior therapy (DBT) as a first treatment step. DBT combines cognitive behavioral and mindfulness techniques and provides patients with skills to deal with emotion regulation, ruminative thinking, and urges to use substances. There are other treatments that also may be helpful in getting patients prepared for trauma-focused therapy. On the other hand, we find that many patients are ready to engage in the trauma-focused psychotherapy early in their treatment, so we should not hesitate to make such therapies available to them.

CATR: Let's shift gears a bit and talk about meds. Are there any meds to consider or avoid alongside psychotherapy?
Dr. Vojvoda: There currently are no medications that are proven to treat both PTSD and SUD. However, there are several effective medications for the treatment of PTSD and SUD when occurring alone, and they have shown some promise in treating this comorbidity. For example, if we have a patient with prominent PTSD symptoms, we will treat that patient with an SSRI, which is currently the most effective medication for trauma-related symptoms. Unfortunately, SSRIs do not improve alcohol use disorder (AUD) in the context of PTSD (Brady KS et al, *J Clin Psychiatry* 1995;56:502–505). But of course, there is evidence that medications like naltrexone and disulfiram improve outcomes in AUD. And so, the combination of an SSRI and one of those medications may be clinically appropriate in patients with comorbid PTSD and SUD.

CATR: So, would you say that SSRIs are a first-line treatment for PTSD, or are they best reserved for people who have not benefitted from a trauma-focused psychotherapy?
Dr. Vojvoda: Clinical practice guidelines for PTSD have recommended both trauma-focused psychotherapies and SSRIs as effective treatments. However, the evidence for the effectiveness of trauma-focused psychotherapy for PTSD is stronger than for antidepressants. For a patient who is open to the idea of trauma-focused therapy, that should be the first-line treatment. However, we often see PTSD patients who have more complex presentations, including prominent depressive or anxiety symptoms. In such cases, we will initiate an SSRI right at the start of treatment, while still trying to engage the patient in the evidence-based therapy. There are also some patients who are not open to the idea of therapy, and for them an SSRI will be the treatment of choice. So, all treatment decisions need to be made in discussion with the patient.

CATR: And for a patient who is willing to engage in psychotherapy, would an SSRI add anything?
Dr. Vojvoda: The most common treatment practice for patients with PTSD is combined medication and psychotherapy treatment. There still are many unanswered questions about choosing and combining treatments. For example, a recent study in combat veterans didn't find a difference in PTSD outcomes between sertraline, PE, and their combination (Rauch SA, *JAMA Psychiatry* 2019;76(2):117–126).

CATR: Speaking of integrating meds with psychotherapy, there's the PTSD-AUD paper from 2013 by Foa and coauthors (https://jamanetwork.com/journals/jama/article-abstract/1724275). I recall it looking at naltrexone, PE, and the combination for both PTSD and drinking outcomes. Your thoughts on the findings?

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Expert Interview – Co-Occurring Addiction and PTSD

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Dr. Vojvoda: That was an interesting study, examining the efficacy of an evidence-based treatment for AUD (naltrexone) combined with an evidence-based treatment for PTSD (PE). Surprisingly, at the end of the study, PTSD severity was reduced across all treatment groups. Naltrexone was effective in reducing the severity of AUD, which was an expected outcome. At the 6-month follow-up, there was an increase in percentage of drinking in all treatment groups, but that increase was smallest in the PE and naltrexone group. This finding, for me, underlines the importance of treating PTSD and SUD simultaneously, as there seem to be long-term benefits for both disorders from such a treatment approach.

CATR: Interesting. Another medication we've been hearing about is prazosin.

Dr. Vojvoda: Yes, anecdotal evidence and early studies of prazosin have shown great promise in the treatment of PTSD, especially in alleviating nightmares and improving sleep. As a result, prazosin was widely prescribed to patients with PTSD, especially in the VA system. Disappointingly, the most recent and largest study did not find prazosin to be effective in reducing nightmares and alleviating sleep disturbance. In another study, prazosin was not superior to placebo in reducing PTSD or AUD. Despite these findings, many psychiatrists continue to prescribe prazosin.

CATR: What about "traditional" meds for SUDs? Can they have any effect on reducing comorbid PTSD symptoms?

Dr. Vojvoda: A 2006 study by Petrakis and others evaluated medications that have been successfully used in treatment of AUD, naltrexone and disulfiram, in patients with comorbid PTSD. Both medications showed evidence for improving PTSD symptoms in addition to improved drinking outcomes (Petrakis IL et al, *Biol Psychiatry* 2006;60(7):777–783). However, a more recent study of adjunctive naltrexone to antidepressant medication did not show an advantage for alcohol use outcomes or PTSD symptoms (Petrakis IL et al, *Neuropsychopharmacology* 2012;37(4):996–1004). At this point, the strongest evidence is for the anticonvulsant topiramate in a couple of studies that showed both a significant decrease in PTSD symptoms and a reduction in alcohol intake. Unfortunately, significant cognitive side effects limit topiramate use. We need more studies of these medications.

CATR: What are your thoughts on using benzos for PTSD?

Dr. Vojvoda: They are best avoided. Benzos are not only contraindicated in terms of risk for substance misuse, they are also not beneficial for PTSD symptoms. If anything, they can increase the symptomology.

CATR: What about antipsychotics?

Dr. Vojvoda: After several encouraging case reports and open studies of antipsychotics, most notably risperidone, there was hope that these medications could be used successfully in treatment of PTSD. However, a large, double-blind study did not support that (Krystal JH et al, *JAMA* 2011;306(5):493–502). At this time, we don't think that there's a role for antipsychotics in the treatment of patients with PTSD, unless they have associated psychotic symptoms.

CATR: Sometimes, re-experiencing is misdiagnosed as psychosis. Do you have any advice to help clinicians differentiate between the two?

Dr. Vojvoda: Patients who are reporting re-experiencing symptoms typically have intact reality testing and are able to report the symptoms as reliving of a traumatic event.

CATR: Any additional advice for the busy clinician?

Dr. Vojvoda: I'll go back to the point about approaching the treatment of SUD and PTSD simultaneously but taking the patient's preference into account when selecting treatment. We as clinicians are often eager to recommend what we believe are the most effective treatments. But starting trauma-focused evidence-based treatment in a patient who's not ready is not helpful and can lead to dropout. The best treatment plans are developed with the patient's input.

CATR: Thank you for your time, Dr. Vojvoda.

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Cognitive Behavioral Therapy for Substance Use Disorders

Continued from page 4

upon that motivation by connecting the patient with group or individual therapy providers.

To learn more about structured CBT sessions and how to incorporate the basics of functional analysis and skill building into your practice, there are some free resources available online. While CBT skills can be applied to recovery from any substance, the National Institute on Alcohol Abuse and Alcoholism has a guide specifically for alcohol use disorder treatment (https://archives.drugabuse.gov/sites/default/files/cbt.pdf). The National Institute on Drug Abuse has a similar guide for cocaine use disorder (https://pubs.niaaa.nih.gov/publications/projectmatch/match03.pdf). Finally, for other ideas on how to incorporate CBT techniques into a medication management visit, the APA offers a book worth checking out (Wright JH, Sudak DM, Turkington D, Thase ME, eds. *High-Yield Cognitive-Behavior Therapy for Brief Sessions: An Illustrated Guide.* Arlington, VA: American Psychiatric Association Publishing; 2010).

CATR VERDICT: CBT skills are easy to learn and evidence-based to promote recovery from addiction. It's definitely worth the time to familiarize yourself with the core concepts of functional analysis and skill building. Learn a few CBT exercises that are high-yield for your patient population as part of your clinical arsenal. These CBT interventions can easily be incorporated into the time frame of medication management visits.

Research Updates

OPIOIDS

Oral vs Extended-Release Naltrexone for Opioid Use Disorder

REVIEW OF: Sullivan MA et al, *Am J Psychiatry* 2017;174(5):459–467

Extended-release (XR) naltrexone (Vivitrol) is FDA approved for opioid use disorder and has shown efficacy in several trials. It works best for patients who have already successfully detoxed from opioids and who are highly motivated to abstain. But what about oral naltrexone? While it is effective for alcohol use disorder, studies for opioid use disorder have shown limited utility. The reason is obvious—patients who are craving a fix can simply skip a dose of the naltrexone pill in order to achieve an opioid high, whereas the XR formulation forces a long delay, during which patients might reconsider their decision to use. Oddly enough, though, no study has been done comparing oral to XR naltrexone, until now.

Researchers randomized 60 adults with opioid use disorder (DSM-IV opioid dependence) to either oral or XR naltrexone. The study was a 6-month open-label trial, excluding people with unstable medical or psychiatric disorders, physical dependence on alcohol or sedative-hypnotics, treatment with opioids or psychotropic medications, and history of opioid overdose in the prior 3 years. The primary outcome measure was retention in treatment.

The study didn't quite mimic real-world treatment, as study participants in both groups were asked to attend behavioral therapy sessions twice weekly, and those randomized to oral naltrexone either had to have a responsible adult as an involved medication monitor at home or go to the clinic 3 times weekly to have it administered. Vouchers were used to reinforce attendance. Participants were mostly white (63.3%), male (83.3%), and in their late 30s (mean age 39.5, SD = 11.1).

At the end of 6 months, the retention rate in the XR naltrexone group was significantly higher than the oral naltrexone group (57.1% and 28.1%, respectively). There was no significant difference in the percentage of opioid-positive urine tests between the groups, though that was not the primary outcome, and missed urine tests were not counted as positive.

Overall, the treatment was well tolerated, and most adverse events reflected opioid withdrawal and gradually improved.

CATR'S TAKE

The results confirm that XR naltrexone is more effective than oral naltrexone, even when rigorous strategies are used to ensure adherence with the oral formulation. We still recommend reserving XR naltrexone for patients who cannot be on buprenorphine or methadone—medications for which we have even more robust data.

—Jessica Goren, PharmD. Dr. Goren has disclosed that she has no relevant financial or other interests in any commercial companies pertaining to this educational activity.

Does Extended-Release Naltrexone Worsen Psychiatric Symptoms?

REVIEW OF: Latif Z et al, *JAMA Psychiatry* 2019;76(2):127–134

Extended-release (XR) naltrexone (Vivitrol) is an injectable version of naltrexone that lasts for 4 weeks and is FDA approved for opioid use disorder (OUD). Although effective, there is some concern that XR naltrexone may cause or worsen psychiatric symptoms because of its opioid blockade. Prior research has been mixed on this issue, and studies have been limited by not comparing XR naltrexone with an active control medication. This new study is the first to directly compare XR naltrexone with buprenorphine in terms of their effects on anxiety, depression, and insomnia.

The outpatient Norwegian study contained two components: a 12-week randomized controlled trial (RCT) and a 36-week follow-up study. In the RCT, 159 participants diagnosed with OUD were randomly assigned, but not blinded, to treatment with flexibly dosed daily buprenorphine/naloxone or monthly injections of XR naltrexone. At the end of 12 weeks, participants could choose treatment with buprenorphine/naloxone or XR naltrexone, and they were then followed for an additional 36 weeks.

Outcome measures included symptoms of anxiety, depression, and insomnia, as assessed by the Hopkins Symptom Checklist and the Insomnia Severity Index. These scales measure symptoms, but they are not diagnostic, and there was no mention of the prevalence and distribution of mood, anxiety, and sleep disorders between the groups.

The results showed that the two treatments were comparable. During the RCT component of this study, XR naltrexone was not significantly different than buprenorphine in terms of anxiety and depression symptoms, and it was slightly better than buprenorphine regarding insomnia symptoms (effect size -0.32; p = 0.008). There were no significant differences between groups in the follow-up component. Encouragingly, throughout all components of the study, anxiety, depression, and insomnia symptoms improved over time.

CATR'S TAKE

It appears that XR naltrexone does not worsen symptoms of anxiety, depression, or insomnia in people with OUD. When we are deciding between XR naltrexone and buprenorphine for OUD, the primary factors should be efficacy and patient access and preference.

—Brian Frankel, MD. Dr. Frankel has disclosed that he has no relevant financial or other interests in any commercial companies pertaining to this educational activity.

CE/CME Post-Test

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Below are the questions for this month's CE/CME post-test. This page is intended as a study guide. Please complete the test online at www.carlataddictiontreatment.com. Note: Learning objectives are listed on page 1.

1. A 36-year-old patient presents with a combination of alcohol and cocaine intoxication and is severely agitated. There is a note in his chart that he also has a history of cardiovascular symptoms. Which of the following medication classes do you choose from as a first-line treatment for his agitation? (LO #1)

   [ ] a. Antipsychotics
   [ ] b. Beta-blockers
   [ ] c. A combination of an antipsychotic and a beta-blocker
   [ ] d. Benzodiazepines

2. What percentage of people in addiction treatment settings typically have a co-occurring psychiatric disorder? (LO #2)

   [ ] a. Less than 10%
   [ ] b. 25%
   [ ] c. 40%
   [ ] d. Over 50%

3. According to a meta-analysis of cognitive behavioral therapy (CBT) for substance use disorders, CBT had the greatest effect size for which of the following substances? (LO #3)

   [ ] a. Marijuana
   [ ] b. Stimulants
   [ ] c. Psychedelics
   [ ] d. Amphetamines

4. In a 2019 study, extended-release (XR) naltrexone was not significantly different than buprenorphine in terms of anxiety and depression symptoms, but was inferior to buprenorphine for insomnia symptoms. (LO #4)

   [ ] a. True
   [ ] b. False

5. In which scenario would buprenorphine be a good first-line choice for a patient with agitation in an emergent setting? (LO #1)

   [ ] a. The patient has symptoms of opioid intoxication
   [ ] b. The patient has both pain and alcohol withdrawal symptoms
   [ ] c. The patient is experiencing symptoms of opioid withdrawal
   [ ] d. The patient has symptoms of cocaine intoxication and opioid craving

6. According to Dr. Ross, which of the following classes of medications would be the best first-line choice for treating schizophrenia that co-occurs with a substance use disorder? (LO #2)

   [ ] a. Typical antipsychotics
   [ ] b. Benzodiazepines
   [ ] c. Atypical antipsychotics
   [ ] d. Mood stabilizers

7. In a 2017 study, retention rates in treatment among XR naltrexone users were significantly higher than among those taking oral naltrexone. (LO #4)

   [ ] a. True
   [ ] b. False

8. Which of the following psychotherapy treatment models has shown the best outcomes for patients with co-occurring addiction and psychiatric disorders? (LO #2)

   [ ] a. Parallel treatment
   [ ] b. Integrated treatment
   [ ] c. Sequential treatment
   [ ] d. Recovery and empowerment model

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Carlat Publishing News

Updates on additional clinical resources we're working on.

The Carlat Psychiatry Report: The May issue features a lead article on the sexual side effects of medications and an Expert Q&A discussing evidence-based dietary plans for managing depression. Our June/July double issue features an Expert QA on the practical management of psychotropic side effects as well as lead articles on auditory hallucinations as well as esketamine.

The Carlat Child Psychiatry Report: The summer double issue features Expert Q&As on the efficacy of medications for depression in children and adolescents and as well as practical approaches to vetting clinical research. The lead article covers transcranial magnetic stimulation (TMS).

Current Book Titles: *The Medication Fact Book for Psychiatric Practice* (Fourth Edition) worth 12 CME credits, *The Child Medication Fact Book for Psychiatric Practice* worth 8 CME credits, *Psychiatry Practice Boosters* (Second Edition) worth 8 CME Credits, and *Addiction Treatment—A Carlat Guide* worth 8 CME Credits. Depending on the title, these books are available with regular binding, spiral binding, and PDF/eBook access.

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